REMARKS/ARGUMENTS

The Status of the Claims

Claims 1, 3-15, 34-44 and 53-67 are pending with entry of this amendment, claim 67 being amended herein. This amendment is made without prejudice and is not to be construed as abandonment or public dedication of the previously claimed subject matter, or agreement with any objection or rejection of record.

With respect to claim 67, support for isolated, synthesized, recombinant and single chain antibodies can be found throughout the specification. For example, see specification at page 5, line 5 though page 6, line 21; page 20, lines 24-30; page 26, lines 2-8 and lines 10-12; page 27, lines 4-32; page 47, lines 9-13; page 46, lines 22-31; page 47, lines 9-10; and Table 1 (pages 59-60). Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

The Claims are Enabled Under the Standard Articulated by Wands: Undue Experimentation is Not Required

Claims 3-13, 39-42 and 61-63 were previously rejected (in the Office Action mailed October 13, 2004) under 35 U.S.C. §112, first paragraph, as allegedly not being enabled because undue experimentation was required to produce the claimed invention. As discussed with the Examiner in the telephonic Interview on February 23, 2005, Applicants provide the following enablement analysis as articulated by In Re Wands 8 USPQ 2nd 1400 (Fed Cir 1988) to demonstrate that the claims are in fact enabled, and that undue experimentation is not required to produce the claimed invention.

Review of In Re Wands

The Wands case sets forth a classic multi-part analysis to be used for determining whether undue experimentation is required in practicing a claimed invention. The analysis is based upon the following eight "Forman" factors (Ex parte Forman 230 USPQ 547):

1) the quantity of experimentation needed
2) the amount of direction or guidance provided by the specification;
3) the presence or absence of working examples;
4) the nature of the invention;
5) the state of the prior art;
6) the relative skill of those in the art;
7) the predictability or unpredictability of the art; and
8) the breadth of the claims.

In understanding how each of the features of this analysis should be applied to the present case, it is instructive to examine the facts and holdings of Wands. The claims at issue in Wands were monoclonal antibody composition claims and method claims employing the monoclonal antibodies; the antibodies were described by their target (hepatitis B surface antigen determinant) and their binding constants (at least 10^9/M). The Patent Office argued that the production of high affinity antibodies was unpredictable, and, therefore, that undue experimentation would have been required to practice the invention. The Court disagreed and struck down the PTO's rejection, setting forth that the Wands application met the enablement requirement of 36 USC §112 and did not require "undue experimentation" even though production and screening of numerous hybridomas was necessary in order to practice the invention.

In addition to finding that Wands was entitled to claims covering a broad class of antibodies (despite the absence of specific sequence information or other structural recitations in the application), the Court sets forth a procedure to be followed by the Office when assessing whether undue experimentation is required in the practice of a given invention. As will be shown in detail below, the present invention meets the enablement requirements as articulated by Wands.

Wands Factor 1: The Quantity of Experimentation is reasonable

The first factor identified by the Court was the quantity of experimentation necessary to practice the claimed invention. As noted in Wands (citing Ex parte Forman),

"The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Applicants submit that the experimentation necessary to practice the claimed invention is reasonable to one of skill in the art. As noted in Wands, screening in order to select desirable antibodies is routine for practitioners of the art. Given the current availability of numerous immunoassay formats, as well as a multitude of platforms for high through-put screening, microscale analyses, and the like, the experimentation involved in testing a series of putative antibody sequences (e.g., those having conservative amino acid substitutions, or differing extents of sequence identity, or various combinations of CDRs as compared to SEQ ID NO: 1 or 2) for epitope binding and internalization is reasonable, and commonplace, to one of skill in the art. Thus, Applicants submit that the first factor for determining enablement has been met, in that the quantity of experimentation necessary to practice the claimed invention is reasonable.

Wands Factor 2: The Direction or Guidance Provided by the Specification is Extensive

The second factor identified by Wands was the amount of direction or guidance presented. The subject specification provides considerable guidance with respect to both production and selection of the internalizing antibodies of the claimed invention. *In vivo* and *ex vivo* processes for producing the claimed antibodies are provided in the specification at, for example, page 13, line 14 through page 14, line 4; page 20 line 24 through page 31, line 2; and in the examples. These methodologies include preparation of antibodies by solid phase chemical synthesis (page 21), recombinant expression (pages 21-25), *ex vivo* production using, for example, a phage display library (pages 25-28); chain shuffling (page 28), site-directed mutagenesis (page 29), and CDR randomization (pages 29-30). In addition, the specification describes numerous techniques that can be employed for recognizing and/or selecting the desired antibodies, including methods for determination of

K_d, competition studies, cross-reactivity with anti-idiotypic antibodies, cross-reactivity studies with F5 and/or C1, and internalization assays (see, for example, page 31, line 4 through page 36, line 31 and within Examples 1-3). Methods for determination of sequence identity (e.g., of antibodies that share at least 70% sequence identity with SEQ ID NO: 1 or SEQ ID NO: 2) are provided at, for example, page 9, line 27 through page 12, line 3. In contrast, Applicants note that only a single screening process was taught in any meaningful way in Wands, and yet the Court still found this comparatively minimal guidance to be adequate direction or guidance for one of skill to practice the Wands' invention.

Applicants submit that, given the extensive teachings of the subject specification, especially as compared to the teaching in Wands, the direction or guidance provided by the specification more than meets the requirements of the second factor in a Wands enablement analysis.

Wands Factor 3: Working Examples Are Provided

The third factor for assessing enablement as identified in Wands is the presence (or absence) of working examples. This factor is actually a further aspect of the second factor enumerated in Wands (i.e., the guidance provided in the specification). Applicants note that the specification need not contain a working example (see In re Borkowski and Van Venrooy 422 F.2d 904, 164 USPQ 642, CCPA 1970). However, sequence information for two exemplary internalizing antibodies of the claimed invention, F5 (SEQ ID NO: 1) and C1 (SEQ ID NO: 2), is provided in the subject specification. In comparison, the Wands specification was found to be enabling even though Wands did not provide sequence information for any exemplary antibodies. Applicants submit that subject specification meets the requirements of the third factor in a Wands enablement analysis.

Wands Factor 4: The Nature of the Invention

The fourth factor identified by the Wands court is the "nature of the invention." Applicants note that antibodies have been the subject of several decades of research, and as a result, the general structure of immunoglobulins, the functions of various antibody domains, and the various mechanisms used by a cell in generating antibody

diversity (e.g., via a controlled process of gene rearrangements) are well within the understanding of one of skill. Given that molecular biology techniques such as site-directed mutagenesis, chain shuffling, CDR randomization, sequence identity determination, and the use of phage display libraries are well known in the art, Applicants submit that generation and manipulation of peptide sequences to generate novel sequences having a desired antibody activity is well within the nature of the invention. The considerable advancements made over the last 25 years in the areas of molecular biology and immunology would easily permit the generation and screening of thousands, if not millions, of peptide sequences for a desired property. Furthermore, the availability of various array and high-throughput screening technologies, immunoassay formats, microscale analysis platforms, and antibody library technologies provide various mechanisms for even one of moderate skill in the art to generate and screen for desired antibody activity from a plurality of sequence combinations. Applicants submit that the fourth factor for determining enablement has been met, since the generation of antibody sequences and screening for desired activity is well within the natural scope of antibody research.

Wands Factor 5: The State of the Prior Art

The fifth factor identified by the Wands court is the state of the prior art. The Wands court determined that the state of the prior art was advanced, with "all of the methods required to practice the invention being known." Given that the present invention is also in the field of immunology, this is true for the subject case as well. As with the techniques used by Wands, the basic underlying immunological and molecular biological techniques proposed for production of the internalizing antibodies of the claimed invention are known and available to one of skill in the art. Indeed, given that the Wands application was filed in 1980 and the subsequent assessment of enablement was decided in 1988, it is expected that the state of the prior art at present is considerably more advanced. Applicants submit that, as was the case in Wands, the state of the prior art is advanced, with all of the methods required to practice the subject invention being known, thus meeting the requirement of the fifth factor of a Wands enablement analysis.

Wands Factor 6: The Relative Skill of Practitioners in the Field

The sixth factor identified by Wands is the relative skill of practitioners in the field. The level of skill of practitioners in the field was considered "high" for the Wands decision (in 1988). Obviously, it is even higher now, given the rapid pace of development and extensive progress that has occurred in the fields of immunology, molecular biology, and bioinformatics. As indicated by the extensive literature in the art, antibody genes from a variety of organisms have been sequenced, and numerous immunoglobulin constructs and/or artificial antibodies have been generated, both *in vivo* and *in vitro*, by numerous practitioners in the field. Given Applicants' disclosure, any moderately competent person of skill in the art can certainly perform each and every step required to make and screen the claimed antibody compositions (thus meeting the sixth factor for determining enablement).

Wands Factor 7: The Predictability or Unpredictability of the Art

The seventh factor identified by Wands is the predictability or unpredictability of the art. As noted in Wands (and expanded upon above), it is routine for practitioners in the art to screen large numbers of compositions for one or more desired antibody characteristics (binding constant, epitope recognition, internalization, and the like). As such, one of skill in the art would not expect every putative sequence generated during the antibody synthesis process to meet the desired limitations. Thus, some level of unpredictability is inherent and expected in the art.

In Wands, the Patent Office had argued that the "low" observed 2.8% rate of success in screening for antibodies in the case was evidence of unpredictability. However, the Court took a different view, noting that in several of the cases in which an entire overall antibody production screen was performed, at least one antibody was produced. Similarly, using the large (10^9-10^{11} member) phage antibody library described in Example 1 of the specification, a number of positive clones, and between 3-15 different antibodies, were identified for each of fourteen different protein antigens, including the c-erbB2 receptor (see Table 1). These results were obtained for a library of sequences generated from diverse V_H and V_L gene repertoires. Had the diversity in sequence been less among members of a similarly-sized library (for example, if the member sequences varied from a sequence known

to have activity, such as SEQ ID NOS: 1 or 2, due to , e.g., conservative substitutions), the number of positive hits would possibly have been greater than when starting with an "unstacked" deck.

In Wands, the Court indicated that even a low success rate would not lead to a conclusion of undue experimentation. Applicants note that a certain level of unpredictability in generating operative embodiments in the present case was not a bar to enablement of at least two operative embodiments (SEQ ID NO: 1 and 2). Since it is routine for practitioners in the art to screen large numbers of compositions for one or more desired antibody characteristics (binding constant, epitope recognition, internalization, and the like), and since the effort involved in assessing large numbers of sequences is lessened by the numerous platforms and assay formats available for high through-put screening, Applicants submit that even a relatively high level of unpredictability (e.g., the need to screen a large number of putative sequences when expecting a small number of positive hits) would not be a deterrent for one of skill given the tools available in the art. Thus, Applicants submit that, as seen in Wands, the unpredictability in the art does not preclude enablement of the invention.

Wands Factor 8: The Breadth of the Claims is Commensurate with Applicant's Teachings

The eighth factor identified by Wands was the breadth of the claims. In Wands, the claims essentially covered the entire universe of possible IgM antibodies that specifically bound hepatitis B surface antigen with a binding constant of at least 10^9/M. While the Office argued that Wands' antibody claims were unduly broad because only a few examples were proven to fall within the scope of the claim, *the controlling majority of the Court found these claims were enabled*, even absent specific sequence information for the few embodiments provided. In doing so, the Court also establishing a precedent regarding the allowable breadth of antibody claims.

As was found to be the case in Wands, the breadth of the pending claims in the subject application is commensurate with the teachings in the specification. As noted above, the methods for producing the putative antibody sequences (e.g., those having conservative amino acid substitutions, or differing extents of sequence identity, or various combinations of CDRs as compared to SEQ ID NO: 1 or 2) are provided in great detail in the

specification. The experimentation involved in testing the resulting antibody sequences for epitope binding and internalization is routine to one of skill in the art. Applicant submit that the teachings of the subject specification are in fact greater than that provided by Wands. Given that the Court found the breadth of the claims in Wands allowable, Applicants submit that the subject specification more than meets the requirement of the eight factor regarding enablement.

Conclusions regarding Enablement

In Wands, the court determined that "When the Wands' data is interpreted in a reasonable manner, analysis considering the facts enumerated in Ex parte Forman leads to the conclusion that undue experimentation would not be required to practice the invention. Wand's disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." (Wands at 1406)

Applicants submit that the facts of the subject application closely parallel that of Wands: the subject specification provides considerable guidance on how to generate and screen for the internalizing antibodies of the invention, there is an even higher level of skill in the art in the late 1990's (the time when the application was filed) than in the early 1980's (when Wands was filed), and all of the methods needed to practice the invention were well known. The above analysis of the Wands factors, taking the true nature of the analysis as applied to the classic Wands case and Applicant's claims, clearly shows that Applicants have taught one of skill how to make and use the invention. Indeed, the present case more than meets the standard for enablement as articulated by the Court. In light of this analysis, Applicants propose that, as with Wands, undue experimentation would not be required to practice the claimed invention. Applicants submit that the rejection under 35 USC §112, first paragraph is improper and respectfully request that it be withdrawn.

F5 and C1 bind to a Different Epitope than TA1 or Herceptin ®

Claims 1, 34-38, 53-57, 59-60 and 67 were previously rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Xu et al. (Int. J. Cancer 53:401-408, 1993) and further in view of Bird et al. (Science 242:423-426, 1988). Applicants traverse.

As noted in the response filed January 13, 2005, the Xu publication does not teach or describe the limitation of the claimed invention, e.g., an internalizing antibody that recognizes the F5/C1-binding epitope of c-erbB2 receptor. Neither Bird nor Chaudhary remedy this deficit. Applicants respectfully submit that the claimed invention is not rendered unpatentable over Xu et al. further in view of Bird et al. and Chaudhary et al. because the cited references do not teach the limitations of the claims. In further support of this traversal, Applicants provide a Expert Declaration from Dr. James Marks showing that the TA1 antibody cited in the prior art binds to a different epitope than the antibodies of the claimed invention. Applicants respectfully submit that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is respectfully requested. Please telephone the undersigned at (510) 769-3511 to schedule an interview.

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Respectfully submitted,

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Attachments:

1) A transmittal sheet;
2) Expert Declaration from Dr. James Marks and accompanying biographical sketch; and
3) A receipt indication postcard.